

SUPPLEMENTAL MATERIAL

Table S1. Definition of co-morbidities

Co-morbidities at entry	ICD-codes (Patient registry) occurring within the last 5 years or or ATC-code (Swedish Drug Prescription registry) within the last 6 months to study entry
Heart failure	I50, I110, I130, I132, I255, K761, I42-43 and purchase of diuretics (ATC: C03)
Valvular disease	I342, I050, I052, Q232, Z952
Other valvular disease	I34-39 except I342, Z953
Prosthetic heart valve (biological)	Z953
Prosthetic heart valve (mechanic)	Z952
Pacemaker or ICD	Z950, Z450 or procedure code FPE
Hypertension	I10-15 or purchase of antihypertensive drugs (ATC: C02)
Diabetes	E10-14 or purchase of antidiabetic drugs (ATC:A10)
Liver disease	K70-77 or procedure codes JJB, JJC
Chronic obstructive pulmonary disease	J43-44
Cancer	Any diagnosis in the C domain of ICD-10
Alcohol use, via the Swedish alcohol index	E244, F10, G312, G621, G721, I426, K292, K70, K860, O354, P043, Q860, T51, Y90-91, Z502, Z714
Dementia	F00-03
Intracranial bleeding	I60-62, S064-066, I690-692
Gastrointestinal bleeding	I850, I983, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K284, K286, K290, K625, K661, K920, K921, K922
Urogenital bleeding	N02, R319, N95
Other bleeding	H431, R04, R58, D629, or procedure code DR029
Coagulation or platelet defect	D65-69
Anaemia	D50-64
Ischaemic stroke	I63, I693
Unspecified stroke	I64, I694
Transient ischaemic attack	G45
Peripheral systemic embolism	I74
Composite thromboembolism	I63-64, G45, I74, I693, I694
Pulmonary embolism	I26
Deep venous thrombosis	I801-802
Composite venous thromboembolism	I26, I801-802
Myocardial infarction	I21, I252
Ischaemic heart disease	I20-25
PCI-procedure procedure code	FNG
CABG-procedure procedure codes	FNA, FNB, FNC, FND, FNE, FNF, FNH
Peripheral arterial disease	I70-73
Vascular disease	I21, I252, I70-73

Table S2. Medication collected from the pharmacy obtained from the Swedish Drug Prescription Registry

Exposure medication	ATC-code (Swedish Drug Prescriptioin registry)
Warfarin	B01AA03
Medication use at study inclusion date (first warfarin purchase-date) or within the preceding 6 months	ATC-code
Aspirin	B01AC06
Clopidogrel	B01AC04
Dipyridamole	B01AC07
NSAID	M01A
Paracetamol	N02BE01
Statins	C10AA
Antidepressant: Selective Serotonin Re-uptake inhibitor (SSRI)	N06AB
Proton pump inhibitor	A02BC
Amiodarone	C01BD01
Macrolide	J01FA
Quinolone	J01M
Combinations of sulfonamides and trimethoprim	J01EE

Table S3. Definition of CHA₂DS₂-VASc and HAS-BLED score

CHA₂DS₂-VASc score	Points	ICD-codes from Patient registry ATC-codes from Drug Prescription registry
Congestive heart failure	1 point	I10-15 or purchase of antihypertensive drugs (ATC: C02)
Hypertension	1 point	I10-15 or purchase of antihypertensive drugs (ATC: C02)
Age >75 years	2 points	
Diabetes	1 point	E10-14 or purchase of antidiabetic drugs (ATC:A10)
Stroke/Transient ischemic attack/ Unspecified stroke/ Systemic thromboembolism/Pulmonary embolism/Deep venous thrombosis	2 point	Stroke/TIA: I63, I693, I64, I694, G45 Peripheral/systemic embolism: I74, I63-64, G45, I74, I693, I694, I26, I801-802
Vascular disease	1 point	Previous MI/Ischemic heart disease: I21,I252, I21,I252 Vascular disease: I21, I252, I70-73 Peripheral arterial disease: I70-73
Age 65-75 years	1 point	
Sex Category: female gender	1 point	
HAS-BLED score	Points	
Hypertension	1 point	I10-15 or purchase of antihypertensive drugs (ATC: C02)
Abnormal liver och renal function	1 or 2 points	Liver disease: K70-77 or procedure codes JJB, JJC Renal function: estimated glomerular filtration rate \leq 60 ml/min/1.73 m ² /or dialysis
Stroke	1 point	Ischemic stroke: I63, I693 Unspecified stroke: I64, I694
Bleeding	1 point	Intracranial bleeding: I60-62, S064-066, I690-692 Gastrointestinal bleeding: I850, I983, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K284, K286, K290, K625, K661, K920, K921, K922 Urogenital bleeding: N02, R319, N95 Other bleeding: H431, R04, R58, D629, or procedure code DR029
Labile INR (TTR<60%)	1 point	Not available (all included patients were 1st time warfarin users)
Elderly (age \geq 65 years)	1 point	
Drugs or alcohol abuse	1 or 2 points	Antiplatelet/NSAID: ATC-code: B01/M01A Alcohol abuse: E244, F10, G312, G621, G721, I426, K292, K70, K860, O354, P043, Q860, T51, Y90-91, Z502, Z714

Table S4. Definition of events during follow-up

Definition of outcomes during follow-up	ICD 10-code (Patient registry)
Intracranial bleeding	I60-62, S064-066, I690-692
Ischemic stroke	I63, I693
Myocardial infarction	I21, I252
	Population-registry
Death	Date of death

Table S5. Sensitivity analysis (TTR based on first 90 days): Time-in-therapeutic range (TTR) in the different renal function categories

	All	eGFR \geq 60	eGFR 45-59	eGFR 30-44	eGFR <30 or dialysis	p-value
N	7577	5596	1324	495	162	
TTR %, median (IQR)	82 (64-96)	82 (65-96)	81 (65-97)	81 (61-95)	71 (55-86)	<0.001
TTR %, mean (SD)	77 (23)	77 (23)	77 (22)	75 (25)	68 (24)	<0.001
TTR in categories						
TTR >75%, n (%)	4567 (60.3%)	3409 (60.9%)	799 (60.3%)	289 (58.4%)	70 (43.2%)	<0.001
TTR 60-75%, n (%)	1486 (19.6%)	1085 (19.4%)	267 (20.2%)	93 (18.8%)	41 (25.3%)	
TTR <60%, n (%)	1524 (20.1%)	1102 (19.7%)	258 (19.5%)	113 (22.8%)	51 (31.5%)	
Number of INR measurement, median (IQR)	8 (5-11)	8 (5-11)	8 (5-11)	7 (5-11)	8 (6-11)	0.240
Median number of days on warfarin, median (IQR)	79 (67-88)	80 (68-85)	79 (66-85)	80 (70-85)	77 (63-84)	0.279
Median (IQR) number of days passing between each INR	9 (6-12)	8 (6-12)	9 (6-12)	9 (7-13)	9 (6-12)	0.079
% (IQR) of INR measurements above 3	0 (0-20)	0 (0-19)	8 (0-22)	9 (0-25)	9 (0-22)	<0.001
% (IQR) of INR measurements below 2	20 (0-36)	20 (0-36)	20 (0-33)	20 (0-33)	29 (14-50)	<0.001

Table S6. Sensitivity analysis (TTR based on first 90 days): Proportion of single and composite study outcomes across eGFR strata

Level	eGFR \geq 60	eGFR 45-59	eGFR 30-44	eGFR <30 or dialysis	p-value
Single endpoints	5596	1324	495	162	
ICH	45 (0.8%)	16 (1.2%)	3 (0.6%)	1 (0.6%)	<0.001
Ischemic stroke	129 (2.3%)	41 (3.1%)	13 (2.6%)	6 (3.7%)	
MI	24 (0.4%)	9 (0.7%)	10 (2.0%)	1 (0.6%)	
Death	208 (3.7%)	86 (6.5%)	60 (12.1%)	31 (19.1%)	
Combined endpoint					
ICH/Ischemic stroke/MI/Death	406 (7.3%)	152 (11.5%)	86 (17.4%)	39 (24.1%)	<0.001

ICH: Intracranial hemorrhage; MI: Myocardial infarction.

Table S7. Sensitivity analysis (TTR based on first 90 days): Multivariable Cox regression analysis of factors associated with the composite endpoint of intracranial hemorrhage, ischemic stroke, myocardial infarction and death (n=7577)

	HR (95% CI)	p-value*
Renal function (ml/min/1.73m ²)		
eGFR ≥60	1.0 (ref)	
eGFR 45-59	1.06 (0.87-1.29)	0.545
eGFR 30-44	1.26 (0.98-1.62)	0.074
eGFR <30, or dialysis	1.69 (1.20-2.39)	0.003
Time in therapeutic range (TTR)		
TTR ≥75%	1.0 (ref)	
TTR 60-75%	1.52 (1.25-1.83)	<0.001
TTR <60%	1.88 (1.58-2.24)	<0.001
Age (years)		
< 65 years	1.0 (ref)	
65-74 years	1.56 (1.19-2.06)	0.001
75-84 years	2.75 (2.11-3.57)	<0.001
≥ 85 years	3.77 (2.77-5.14)	<0.001
Female	1.00 (0.85-1.16)	0.995
Diabetes	1.32 (1.08-1.60)	0.006
Hypertension	1.01 (0.86-1.19)	0.890
Vascular disease (prior myocardial infarction, ischemic heart disease, or peripheral arterial disease)	1.33 (1.09-1.62)	0.006
Heart failure	1.72 (1.39-2.11)	<0.001
Valvular disease	1.17 (0.65-2.11)	0.595
Cancer within last 3 years	1.22 (1.01-1.49)	0.047
Coagulation/platelet defect	1.19 (0.56-2.52)	0.650
Anemia	1.17 (0.86-1.58)	0.376
Ischemic stroke	1.04 (0.71-1.47)	0.832
Prior systemic emboli	1.11 (0.81-1.53)	0.507
Deep vein thrombosis/Pulmonary embolism	1.52 (1.18-1.95)	0.001
Prior intracranial hemorrhage	1.78 (0.79-4.02)	0.001
Prior gastrointestinal bleeding	0.93 (0.51-1.69)	0.807
Antiplatelet therapy	1.05 (0.89-1.24)	0.549

* Interaction terms tested: age and eGFR: p=0.044; age and TTR, p =0.244; eGFR and TTR, p=0.804.

Figure S1. Sensitivity analysis: Association of TTR and renal function to outcome. Kaplan-Meier curve: time-in-therapeutic range and association to outcome
 Outcome is a composite of intracranial hemorrhage/ischemic stroke/myocardial infarction/death.

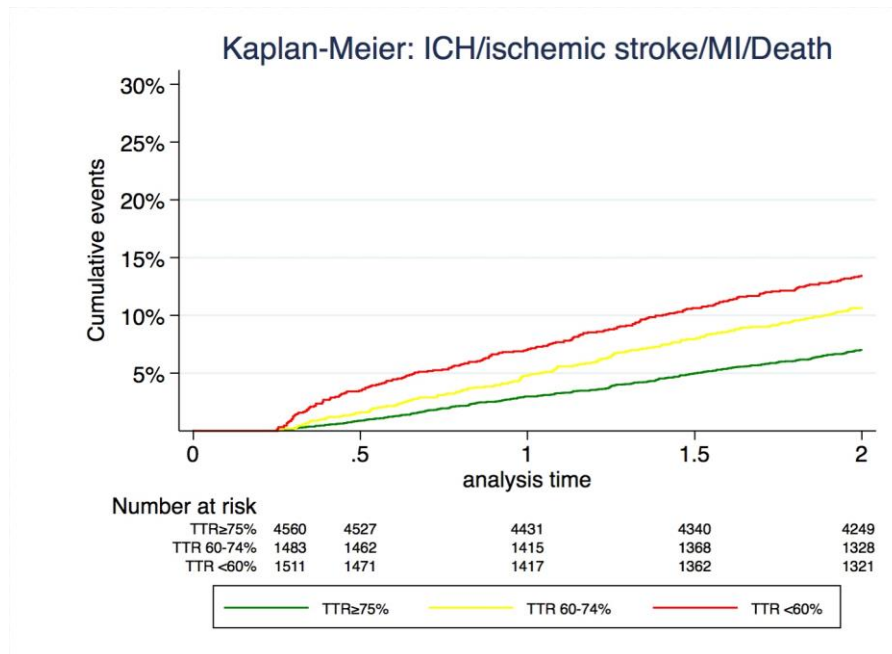


Figure S2. Kaplan-Meier curve for combined eGFR and TTR groups:

